

Exceptional Case

Acute Epstein–Barr virus infection-associated collapsing glomerulopathy

Amit Joshi¹, Amit Arora², David Cimbaluk³, George Dunea² and Peter Hart¹

¹Division of Nephrology, John H. Stroger Hospital of Cook County, Chicago, IL, USA, ²University of Illinois at Chicago, Chicago, IL, USA and ³Department of Pathology, Rush University Medical Center, Chicago, IL, USA

Correspondence and offprint requests to: Amit Joshi; E-mail: ajoshi@cookcountyhhs.org

Abstract

A 21-year-old woman presenting with acute Epstein–Barr virus (EBV) infection (infectious mononucleosis) was noted to have renal involvement. She had proteinuria, leukocyturia and microscopic hematuria, and 10 days after admission became nephrotic (23 g of protein per g of creatinine). Renal biopsy revealed glomerular tuft collapse, visceral epithelial cell proliferation and vacuolization consistent with collapsing glomerulopathy. She had only transient deterioration in renal function, attributed to contrast nephropathy, but after recovery remained proteinuric. Renal disease is well described in EBV infection, but collapsing glomerulopathy has not been reported previously.

Keywords: collapsing glomerulopathy; infectious mononucleosis; nephrotic syndrome

Background

Collapsing glomerulopathy has been recognized as a form of focal segmental glomerulosclerosis characterized by collapse of the glomerular capillary tuft and proliferation of the visceral epithelial cells. Most cases have been seen in patients with HIV infection, but since 1986 an association with several non-HIV-related conditions has also been reported [1–3]. Indeed, as early as in 1999, one center reported that as many as two-thirds of cases of collapsing glomerulopathy (collapsing GN) were non-HIV-related; labeled as collapsing idiopathic GN [4]. It is now known that collapsing GN may occur in association with viruses (parvovirus B19, cytomegalovirus (CMV), HTLV-1 and HCV), bacteria (tuberculosis), parasites (leishmaniasis), febrile illness, drugs (interferon alpha, pamidronate), autoimmune diseases, malignancy (acute monoblastic leukemia, multiple myeloma, hemophagocytic syndrome), post-transplantation and certain genetic causes [5].

Case report

A previously healthy 21-year-old African-American woman presented with a 4-day history of malaise, fever, nausea, vomiting, anorexia and left-sided abdominal pain. The patient, a thin woman with BMI of 21.0 kg/m², had a temperature of 38.9°C (102°F), pulse rate of 100 bpm, respiratory rate of 22 per minute and blood pressure of 110/70 mmHg. The spleen was markedly

enlarged and there was tenderness over the left upper abdominal quadrant. There was no skin rash, regional lymphadenopathy, pharyngitis or tonsillitis. Initial laboratory tests were significant for a normocytic normochromic anemia [hemoglobin 5.8 g/dL (58 g/L)], thrombocytopenia (platelet count 103 000 cells/μL) and a lymphocyte count of 4400 cells/μL (normal 1200–3400 cells/μL). CT scan of the abdomen (without intravenous contrast) revealed massive splenomegaly and hypodensities suggestive of infarcts.

Autoimmune workup including serum antinuclear antibodies, antineutrophil cytoplasmic antibodies, complements, antiphospholipid antibodies, serum and urine protein electrophoresis with immunofixation were normal. Testing for lymphoproliferative diseases revealed normal flow cytometry, absent JAK 2 mutation, no bcr/abl gene translocation and unremarkable bone marrow biopsy. Infectious workup was negative for human immunodeficiency virus (HIV) 1 and 2 serology, and HIV RNA by polymerase chain reaction (PCR). CMV IgG was positive with absent IgM titers. Hepatitis B and C serologies, urine histoplasma antigen, serum rapid plasma reagin and Parvovirus B19 were negative. A transthoracic echocardiogram was normal without evidence of vegetations. The monospot test on the day of admission was negative. Epstein–Barr virus (EBV) DNA and viremia (as assessed by qualitative PCR methods) was reported as positive on day 9. Subsequent testing for EBV-specific antibodies revealed positive IgM VCA (viral capsid antigen) titers (>1:10) and positive IgG VCA on day 10.

On admission, blood urea nitrogen (BUN) was 2.5 mmol/L (7 mg/dL), and serum creatinine was 53 μmol/L

(0.6 mg/dL). Urinalysis showed specific gravity of 1.019, 1+ dipstick proteinuria, 5 red blood cells, and 15 white blood cells per high power field magnification (hpf), no cellular casts and sterile urine culture. No previous baseline values were available for comparison. At the time of renal consultation on day 10 of admission, serum creatinine had increased to 133 $\mu\text{mol/L}$ (1.5 mg/dL) 24 h after administration of intravenous contrast for a repeat CT scan of the abdomen. Imaging showed increasing splenomegaly and infarcts involving >50% of the spleen. Repeat urinalysis revealed a specific gravity of 1.036, 4+ dipstick proteinuria, 5 red blood cells and 215 white blood cells per hpf, sterile urine culture and a spot urine protein to creatinine ratio of 23, confirmed on two separate occasions. Urine microscopy revealed leukocyturia with white blood cell casts. Serum albumin had dropped to 12 g/L (1.2 g/dL) from a baseline of 32 g/L (3.2 g/dL), and total cholesterol had increased to 4.8 mmol/L (185 mg/dL) from a baseline 2.2 mmol/L (85 mg/dL).

Renal biopsy was performed on day 15 to characterize the new-onset nephrotic syndrome as the patient had now also developed anasarca. It revealed collapse of the glomerular capillary tuft, visceral epithelial cell proliferation and vacuolization consistent with collapsing glomerulopathy (Figure 1), alongside with evidence of recovering acute tubular necrosis. *In situ* hybridization for EBV was negative.

On day 18, a therapeutic splenectomy was performed because of unremitting abdominal pain and radiologic evidence of capsular rupture. Splenic tissue examination showed multifocal infarction, capsular rupture and confirmed the presence of EBV-encoded RNA (EBER) by *in situ* hybridization (Figure 2). After splenectomy, the fever and abdominal pain completely resolved. Serum creatinine returned to a baseline of 53 $\mu\text{mol/L}$ (0.6 mg/dL) on day 20. Follow-up EBV serology on day 21 revealed positive IgG EBNA (Epstein–Barr nuclear antigen) titers. RAAS blockade (enalapril) was initiated for sustained proteinuria. Subsequent follow-up over the next few months showed improving proteinuria, urine sediment and serum albumin levels. At the last clinic visit (11 months after illness onset), serum creatinine was 53 $\mu\text{mol/L}$ (0.6 mg/dL), serum albumin 39 g/L (3.9 g/dL), urine sediment had 1 red blood cell and 1 white blood cell per hpf, and proteinuria had lowered to <1 g/g of creatinine in the urine. The patient continues to be conservatively managed with up-titration of RAAS blockade and is being closely monitored by the clinic.

Discussion

Here we report an association between collapsing glomerulopathy and an acute EBV syndrome, manifesting itself clinically as nephrotic syndrome with massive proteinuria, hypoalbuminemia, anasarca and hypercholesterolemia. The reversible rise in creatinine was most likely due to contrast-induced acute kidney injury, also demonstrated on renal biopsy.

EBV has been associated with several renal syndromes. Evidence of renal involvement is reported in 3–16% of patients with acute infectious mononucleosis [6, 7]. The most commonly described renal lesion has been an acute tubulo-interstitial nephritis [7,8]. Nephrotic syndrome in acute infectious mononucleosis was first published in 1963 in a case in which kidney biopsy was inconclusive [9]. Glomerular lesions have included membranous nephropathy [10, 11], mesangial focal proliferative disease with cellular crescents [12], minimal-change disease [13, 14] and vasculitic lesions such as polyarteritis nodosa [15]. To our knowledge, this is the first report of collapsing glomerulopathy.

EBV predominantly infects B lymphocytes, the producers of immunoglobulin through specific EBV/C3d receptors on B cells [16]. A viral glycoprotein, gp350, bears sequence homology to the C3 complement fragment C3d [16]. One of the main reservoirs of EBV is the nasopharyngeal mucosa [17], where epithelial cells endocytose circulating polymeric IgA-EBV immune complexes by specific receptors and transport them to the luminal surface [18]. EBV is also assumed to replicate in these cells [18]. More than 90% of asymptomatic adults shed EBV in saliva [17]. EBV infection seems to represent equilibrium between viral replication *in vivo* and the host's immune removal of the virus, and disease occurs when there is an imbalance in the host immunity [17].

The mechanism of glomerular disease in EBV is not clear. It could be related to an uptake of immunoglobulin-EBV complexes by glomerular visceral and parietal epithelial cells similar to that in the nasopharyngeal mucosa. Moudgil *et al.* have shown localization of parvovirus B19 DNA (another viral cause of collapsing GN) in glomerular parietal and visceral epithelial cells [19]. Another study suggested a causative role of EBV infection in the pathogenesis of interstitial nephritis [20]. EBV DNA has been detected in renal tissue in IgA nephropathy, membranous nephropathy and focal/segmental lesions; and is quantitatively greater in subgroups with mesangial

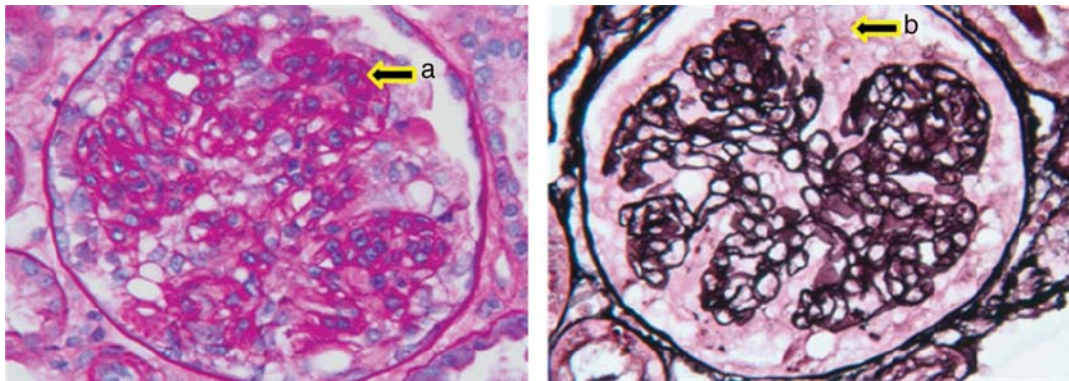


Fig. 1. Collapse of glomerular tuft (a) along with visceral epithelial cell proliferation and vacuolization (b) on PAS (periodic acid-Schiff) and Jones' stain.

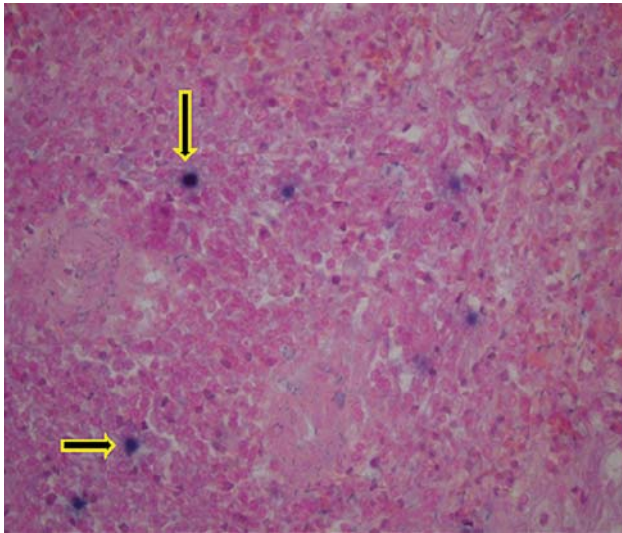


Fig. 2. Splenic tissue with positive Epstein-Barr virus *in situ* hybridization.

injury, fibrinogen deposits and immunoglobulin deposits, suggesting a causative role [21]. Other studies have also reported transformation of B cells by EBV to produce more IgA than IgG, especially in IgA nephropathy, and the same IgA1 subtype that was produced by transformed B cells was found deposited in the glomerular mesangium [22, 23].

In our patient, EBV was detected by *in situ* hybridization in splenic but not renal tissue. This may have been due to a low viral copy number or to the focal nature of the infection. Differences in the detection techniques applying PCR and Southern blot to the extracted DNA may have also contributed to the absence of EBV detection in renal tissue. However, there was a significant association of acute EBV viremia and collapsing GN in our patient. As the acute phase of the infection cleared, proteinuria gradually improved, but persisted, suggesting the possibility of secondary autonomous phase of podocyte loss [24].

Conflict of interest statement. None declared.

References

- Weiss MA, Daquiaoq E, Margolin EG et al. Nephrotic syndrome, progressive irreversible renal failure, and glomerular 'collapse': a new clinicopathologic entity? *Am J Kidney Dis* 1986; 7: 20–8
- Detwiler RK, Falk RJ, Hogan SL et al. Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int* 1994; 45: 1416–24
- Valeri A, Barisoni L, Appel GB et al. Idiopathic collapsing focal segmental glomerulosclerosis: a clinicopathologic study. *Kidney Int* 1996; 50: 1734–46
- Laurinavicius A, Hurwitz S, Rennke HG. Collapsing glomerulopathy in HIV and non-HIV patients: a clinicopathological and follow-up study. *Kidney Int* 1999; 56: 2203–13

- Albaqumi M, Soos TJ, Barisoni L et al. Collapsing glomerulopathy. *J Am Soc Nephrol* 2006; 17: 2854–63
- Wechsler HF, Rosenblum AH, Sills CT. Infectious mononucleosis: report of an epidemic in an Army post. *Ann Intern Med* 1946; 25: 113 passim 236–265.
- Lee S, Kjellstrand CM. Renal disease in infectious mononucleosis. *Clin Nephrol* 1978; 9: 236–40
- Tsai JD, Lee HC, Lin CC et al. Epstein-Barr virus-associated acute renal failure: diagnosis, treatment, and follow-up. *Pediatr Nephrol* 2003; 18: 667–74
- Greenspan G. The nephrotic syndrome complicating infectious mononucleosis. Report of a case. *Calif Med* 1963; 98: 162
- Araya CE, Gonzalez-Peralta RP, Skoda-Smith S et al. Systemic Epstein-Barr virus infection associated with membranous nephropathy in children. *Clin Nephrol* 2006; 65: 160–4
- Meyer P, Soöte S, Raynaud P et al. Acute inflammatory polyradiculoneuropathy and membranous glomerulonephritis following Epstein-Barr virus primary infection in a 12-year-old girl. *Arch Pediatr* 2010; 17: 1535–9 [Article in French]
- Kano K, Yamada Y, Sato Y et al. Glomerulonephritis in a patient with chronic active Epstein-Barr virus infection. *Pediatr Nephrol* 2005; 20: 89–92
- Mikhalkova D, Khanna S, Vaidya R et al. Epstein-Barr virus-associated nephrotic syndrome. *Clin Kidney J* 2012; 5: 50–52
- Berthoux FC, Zech PY, Blanc-Brunat N et al. Association of nephrotic syndrome and Hodgkin's disease. Role of Epstein-Barr virus. *Nouv Presse Med* 1976; 5: 255–8 [Article in French]
- Caldeira T, Meireles C, Cunha F et al. Systemic polyarteritis nodosa associated with acute Epstein-Barr virus infection. *Clin Rheumatol* 2007; 26: 1733–5
- Nemerow GR, Mold C, Schwend VK et al. Identification of gp350 as the viral glycoprotein mediating attachment of Epstein-Barr virus (EBV) to the EBV/C3d receptor of B cells: sequence homology of gp350 and C3 complement fragment C3d. *J Virol* 1987; 61: 1416–20
- Rickinson AB, Yao QY, Wallace LE. The Epstein-Barr virus as a model of virus-host interactions. *Brit Med Bull* 1985; 41: 75–9
- Sixbey JW, Yao QY. Immunoglobulin A-induced shift of Epstein-Barr virus tissue tropism. *Science* 1992; 255: 1578–80
- Moudgil A, Nast CC, Bagga A et al. Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy. *Kidney Int* 2001; 59: 2126–33
- Bao L, Zhang Y, Zheng X. Detection of Epstein-Barr virus DNA in renal tissue from patients with interstitial nephritis. *Zhonghua Nei Ke Za Zhi* 1996; 35: 542–4 [Article in Chinese].
- Iwama H, Horikoshi S, Shirato I et al. Epstein-Barr virus detection in kidney biopsy specimens correlates with glomerular mesangial injury. *Am J Kidney Dis* 1998; 32: 785–93
- Layward L, Allen AC, Harper SJ et al. Increased IgA and decreased IgG production by Epstein-Barr virus-transformed B cells in culture in IgA nephropathy. *Exp Nephrol* 1994; 2: 24–9
- Tomino Y, Koide H, Yagame M et al. Preliminary study on specificity of IgA released from lymphocytes by EB virus transformation in patients with IgA nephropathy. *Am J Med Sci* 1990; 299: 374–8
- Sato Y, Wharram BL, Lee SK et al. Urine podocyte mRNAs mark progression of renal disease. *J Am Soc Nephrol* 2009; 20: 1041–52

Received for publication: 9.4.12; Accepted in revised form: 23.4.12